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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,980	09/30/2003	Yaron Ilan	Enz-64 (CIP)	9089

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EXAMINER	
HORNING, MICHELLE S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/675,980	IIAN ET AL.	
	Examiner	Art Unit	
	Michelle Horning	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-204* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 2-5,7-10,12-42,46,53,55-58,61-74,77-96,98-108,110-118,121-123,129-150,154-156,158-160,171-177,183,185,187,189,190,197,198 and 200-202.

Continuation of Disposition of Claims: Claims rejected are 1,6,11,43-45,47-52,54,59,60,75,76,97,109,119,120,124-128,151-153,157,161-170,178-182,184,186,188,191-196,199,203 and 204.

DETAILED ACTION

This office action is responsive to communication filed 9/1/2006. The status of the claims is as follows: claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97,109, 119-120, 124-128, 151-153, 157, 161-170, 178-182, 184, 186, 188, 191-196, 199 and 203-204 are under current examination and claims 2-5, 7-10, 12-42, 46, 53, 55-58, 61-74, 77-96, 98-108, 110-118, 121-123, 129-150, 154-156, 158-160, 171-177, 183,185, 187, 189-190, 197-198 and 200-202 are drawn to non-elected inventions. All claims 1-204 are pending.

Applicant's election with traverse of Invention I in the reply filed on 9/1/2006 is acknowledged. The traversal is on the ground(s) that T cell ligand and an intermediary metabolite are not necessarily different, given that both are lipids and have polarity. This is not found persuasive because while they share such *generic* elements, these features do not make them similar in scope.

The requirement is still deemed proper and is therefore made FINAL.

Objection to the Specification

The disclosure is objected to because of the following informalities: 1. each page has 2 sets of different page numbers, located at either the bottom center or bottom left of each page; 2. Glucocerebroside is misspelled on page18 (using the center bottom page number).

Appropriate correction is required.

Claim Rejections

35 U.S.C. 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 119-120, 124-125, 127-128, 152-153, 168-170, 182, 188, 196, 199, and 203-204 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 119 recites the limitation "glycolipid" in claim 6. There is insufficient antecedent basis for this limitation in the claim.

Claim 120 recites the limitation "glycolipid" in claim 11. There is insufficient antecedent basis for this limitation in the claim.

Claims 124-125, 127-128 and 152-153 are rejected for depending from either claim 119 or 120.

Claim 168 recites the limitation "monosaccharide ceramide" in claim 45. There is insufficient antecedent basis for this limitation in the claim.

Claim 169 recites the limitation "glycosylceramide" in claim 45. There is insufficient antecedent basis for this limitation in the claim.

Claim 170 recites the limitation "glucosylceramide" in claim 45. There is insufficient antecedent basis for this limitation in the claim.

Claim 182 recites the limitation "administering step" in claim 75. There is insufficient antecedent basis for this limitation in the claim.

Claim 188 recites the limitation "administering step" in claim 109. There is insufficient antecedent basis for this limitation in the claim.

Claim 196 recites the limitation "mammalian subject" in claim 120. There is insufficient antecedent basis for this limitation in the claim.

Claim 199 recites the limitation "administering step" in claim 119. There is insufficient antecedent basis for this limitation in the claim.

Claim 203 recites the limitation "immune-mediated or immune-related disease or disorder" in claim 119. There is insufficient antecedent basis for this limitation in the claim.

Claim 204 recites the limitation " immune-mediated or immune-related disease or disorder " in claim 120. There is insufficient antecedent basis for this limitation in the claim.

35 U.S.C. 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-128, 151-153, 157, 161-166, 168-169, 178-182, 184, 186, 188, 191-196, 199 and 203-204 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for, at most treatment of colitis by administration of glucocerebroside, does not reasonably provide enablement for all mammalian diseases. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the Invention. The claims are drawn to a disease treatment of mammalian subject via administration of an intermediary metabolite. Further, the claims are drawn to either inhibition or stimulation in NKT cell number or function caused by either the displacement or the increased binding of activating elements from/to the CD1d molecule.

State of the prior art. At the time the invention was made, monosaccharide ceramides, such as, glucosylceramides were known in the art to have antitumor and immunostimulatory activities, including suppressing melanoma B16, colon adenocarcinoma and protecting the body against radiation. It was also known in the prior that there are different types of NKT cells, including the CD1d-dependent and the CD1d-independent NKT cells (see Smyth et al 2002).

Breadth of the claims. The claims are extremely broadly, encompassing treatment of any and all diseases in any mammal. The claims are not limited to a delivery of a single type of intermediary metabolite, encompassing the use of all intermediary metabolites. Further, an intermediary metabolite can be anything according to the following definition in the specification (paragraph 43) which reads "the intermediary metabolite includes, but is not limited to a T cell receptor ligand, a lipid, a polar lipid, a conjugated biomolecule, a glycolipid, a lipoprotein, an apolipoprotein, a glycoprotein, a monosaccharide or polysaccharide ceramide, a glucosylceramide, a galactosylceramide, a glucocerebroside, a

glucocerebroside analogue or derivative, a sphingosine, a sphingolipid or a ceramide". The claims do not disclose which population type of NKT cells the invention is drawn to, for example, the CD1d-dependent and the CD1d-independent NKT cells.

Working examples. Examples in the specification of the instant application reveal the effects of glucocerebroside treatment on only few disease examples, including hepatitis, experimental colitis, melanoma and diabetes on mice. In the colitis example, Applicants evaluated the effects of glucocerebroside by determining the following parameters: diarrhea, degree of colonic ulcerations, intestinal and peritoneal adhesions and wall thickness. There are no working examples directed to the underlying mechanism of glucocerebroside-induced effects of either the CD1d molecule or its activating elements. For example, no binding affinity data is disclosed. While Applicants need not to explain how their invention operates, the absence of such information makes it impossible to extrapolate the results obtained with glucocerebroside treatment of colitis to the treatment of other diseases with other drugs.

Guidance in the specification. The specification provides little guidance regarding the practice of the methods as claimed. The specification refers to treatment of specific diseases, many of which were experimentally induced (e.g. colitis), in mice. There is no specific guidance regarding the treatment of all diseases known in all mammalian subjects via administration of all possible intermediary metabolites. Further, the specification provides no evidence regarding the molecular mechanisms of glucocerebroside-induced effects. The

competitive displacement of activating elements from the CD1d molecules and the increased binding of the activating elements to the CD1d molecule are only theories. The specification also fails to provide any evidence showing that the increase or decrease of either number or function of NTK cells is due to the CD1d molecule. The actual activating elements are not disclosed in the specification nor are the type of NTK cells.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). There is no way to predict the therapeutic effect, if any, of all intermediary metabolites in the treatment of all diseases at the molecular level. Further, different diseases have different etiologies and different drugs have different modes of action.

Amount of experimentation necessary. Besides the general expectation that it will require years of further research to develop effective therapy for any disease, it would require extensive research to understand the fundamental biology of the each disease. As claimed, essentially all of the work required to ultimately develop a method of treatment has been left for others including determination of a NKT cell type, a specific activating element and the binding affinities of a specific activating element to CD1d molecule.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 11, 43, 45, 54, 59-60, 75, 97, 109, 119-120, 124-128, 151-153, 157, 168-170, 179-182, 184, 186, 188, 199, 203-204 are rejected under 35 U.S.C. 102(b) as being anticipated by Taniguchi et al (cited in IDS). The limitations of the above claims are: 1) a method for the treatment of disease in a mammal comprising administration of intermediary metabolite; 2) wherein the result comprises a change, more specifically, an increase in the number or function of regulatory, immune-regulatory or NKT cells; 3) wherein at least one component in the immune system is changed; 4) the method further comprises antigens, including autologous antigens; 5) wherein the intermediary metabolite comprises a monosaccharide ceramide, more specifically, a glucosylceramide; 6) wherein the method of administration is intraperitoneal; 7) wherein the glucosylceramide comprises a glucocerebroside; 8) wherein the glucocerebroside is an analogue or derivative; and 9) wherein the disease or disorder is colitis, more specifically, Ulcerative Colitis.

This prior art reference teaches a treatment method in which glycosylceramides and derivatives are used as the active ingredients in activating NKT cells; this method serves as remedies for diseases and disorders, including ulcerative colitis (whole document). The structure of glucocerebroside is

disclosed on page 3. Further, "antigen presenting cells treated with KRN 7000 showed a marked stimulative effect on Vα24+ NKT cell proliferation in a manner dependent on the number of antigen-presenting cells" (page 18, lines 57-58, also see Figure 9 on page 36). Taniguchi et al disclose the use of autologous antigens in the following quote "an autologous mixed leukocyte reaction (MLR) was performed using these antigen-presenting cells as stimulator cells and autologous peripheral blood mononuclear cells as responder cells" (page 18, paragraph 98). Given that Taniguchi et al meet all of the limitations of the above, these claims are rejected.

35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of

35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6, 11, 43-45, 49-52, 59-60, 97, 119, 124, 161-167, 178-179, 199 and 203 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vliet et al (1999) and EP 0 988 860 (2000, hereinafter as "Taniguchi"). The limitations of the claims are: 1) a method for the treatment of disease in a mammalian subject comprising administration of an intermediary metabolite; 2) comprising changes in cytokine responses; 3) resulting in a decrease in the number or function of regulatory, immune-regulatory or NKT cells; 4) resulting in a increase in the number or function of regulatory, immune-regulatory or NKT cells; 5) wherein the change in cytokine responses comprise IFN-gamma, IL2, IL4, IL10 or IL12; 6) wherein the change in cytokine response comprises a pro-inflammatory, anti-inflammatory or both; 7) wherein the result further comprises changes in the Th1/Th2 balance; 8) intraperitoneally administration of intermediary metabolite and 9) the disease or disorder is colitis.

Vliet et al discloses a method in which NKT B cells isolated from human donors are treated with KRN7000 in culture (see entire document). The alteration in cytokine profiles are shown in Tables 1 and 2 demonstrating both an upregulation and a downregulation of specific NKT cell functions. More specifically, the Table 1 reveal an upregulation of both pro-inflammatory IFN-gamma and anti-inflammatory IL-4 expression, thus, leading to a change in the Th1/Th2 balance.

Vliet et al does not teach a method for the treatment of colitis in a mammalian subject with intraperitoneally administration of intermediary metabolites. Taniguchi teaches a method in which NKT cell-activating agents, including galatosylceramides or glucosylceramides, are used for therapeutic agents for diseases, including ulcerative colitis (see whole document, including pages 2 and 3). Further, this prior art reference teaches intraperitoneal administration of intermediary metabolites (see page 9, paragraph 39) comprising glucocerebroside and many of its derivatives (see pages 3-6). It would have been obvious to one of ordinary skill in the art to modify the methods taught by Vliet et al and Taniguchi et al in order to alter the cytokine responses via intraperitoneal administration of an intermediary metabolite to treat mammalian disease. One would have motivated to do so, given the suggestion by Vliet et al, because KRN7000 can be recognized by NK T-cells and trigger cytokine release and thus, "be a useful agent in the modulation of immune responses" (see Discussion). There would have been a reasonable expectation of success, given the knowledge that intermediary metabolites are already administered for mammialian treatment, for example, the "α-glucosylceramide structure protects the body from radiation" as well as "increases the number of platelets and leukocytes" (Taniguchi et al, see paragraph 8). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 191-196 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vliet et al (1999) and EP 0 988 860 (2000, hereinafter as

"Taniguchi"), and further in view of Connolly and Cunningham (2000). As mentioned above, Vleit et al and Taniguchi combined teach a method for the treatment of colitis in a mammalian subject with intraperitoneally administration of intermediary metabolites. These references do not disclose food and/or water deprivation prior to administration of intermediary metabolites. This practice is, however, commonly taught in the prior art by many references including that by Connolly and Cunningham. It would have obvious to one of ordinary skill in the art to modify the methods taught by Vliet et al, Taniguchi and Connolly and Cunningham to incorporate fasting prior to the administration of intermediary metabolites. One would have been motivated to do so, given the suggestion by Connolly and Cunningham, in order to minimize the volume and increase the pH of the gastric contents. There would have been a reasonable expectation of success, given this practice has been advised since the late 19th century (see Connolly and Cunningham). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

DOUBLE PATENTING

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed.

Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 11, 43-45, 59-60, 97, 119-120, 124-125, 151-153, 157, 165-166, 168-169, 179-181, 199 and 203-204 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 10 of copending Application No. 10/375, 906. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method steps in treating a disease in a mammalian subject are identical.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

CONCLUSION

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michelle Horning whose telephone number is

571-272-9036. The examiner can normally be reached on Monday-Friday, 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 570-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for unpublished application is available through Private PAIR only. For more information about PAIR system, see htt://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michelle Horning
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